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**BIOENERGY TECHNOLOGIES OFFICE** 

DOE BioEnergy Technologies Office (BETO) 2023 Project Peer Review

### **Lessons Learned and Introduction to Future Plans**

April 4, 2023 Conversion Technologies

Nathan J. Hillson Berkeley Lab





# **Project Overview**

# **Project History**

- In June 2022, ABF presented to BETO its concept for FY23-25
  - This presentation included a section dedicated to "Lessons Learned from Past Years"
- In September 2022, BETO instructed ABF strategic planning
  - Included guidance regarding the process, timeline, and representative deliverables to focus the process
- In October 2022, the ABF began its strategic planning process
  - Lessons learned from past years (including those presented in June 2022) played a significant role in guiding the strategy developed
  - The strategic planning process also included the formation of a "Reviewing History" working group to assess what worked well and what did not work well historically
- In December 2022, the ABF completed its strategic plan
  - This presentation, in addition to a sampling of lessons learned, will provide an introduction to ABF's future plans
  - The ABF has developed new vision / mission statements, goals, deliverables, and organizational structure (next presentation)





# **Project Goal and BETO Relevance**

- Goal: Apply ABF's past lessons learned, along with the efforts of the reviewing history working group, to inform and guide the development of the revised ABF strategic plan
- Relevance to BETO's goals: This activity, both instructed by BETO
  and a common sense best practice, ensures that the ABF's future
  plans are made wisely
- Specific research question: How to best use past lessons learned when undertaking a strategic re-envisioning of a large multi-lab consortium project with a significant history and established identity in the community?







# 1 – Approach

# **Technical Approach**

- Follow BETO's guidance for ABF strategic planning process
  - Assess what worked well and what did not work well historically, and establish a working group to do this
- Use reflections from lessons learned presented to BETO
  - During June 2022 concept planning meeting
- Use ABF reviewing history working group's outcomes
  - Both during strategic and implementation planning phases
- Develop wise and informed strategic and implementation plans
  - To be presented today
  - Have a strategic planning lead and approach to guide the process





# **Top Potential Challenges**

- Applying lessons learned in a nuanced fashion
  - Just because initial attempts at something didn't turn out well, doesn't mean that the direction is a bad one
  - Make sure that the right lesson is being learned
- Overcoming the temptation to maintain status quo
  - It may be tempting to dismiss concerns when they suggest that a large uncomfortable change should be made
- Applying consensus-driven lessons learned equitably
  - Without disproportionately adversely affecting a small demographic
  - Not all stakeholders (whether internal to the ABF or not) may have been affected equally
- Charting an ambitious vision for the ABF
  - That is measurable and achievable



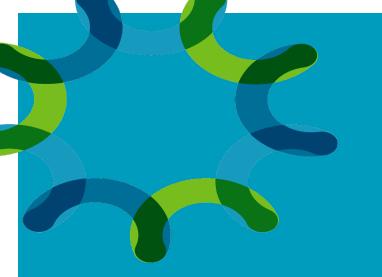


# **Advisory Board**

#### Advisory Board

- Contributes to the ABF maintaining relevance and understanding pain points and innovations
- Acts as a sounding board for feedback on ABF progress (including lessons learned) and future plans to ensure
  efforts are industrially relevant





# 2 - Progress and Outcomes

# Tracking DBTL cycle efficiency metrics

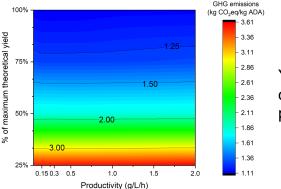
- What happened?: DBTL cycle tracking efforts did not enable the ABF to quantify the reduction in bioprocess development time in the way that had been originally envisioned. There were no standard definitions for DBTL cycle efficiency. Not all DBTL cycles used the same unit operations. ABF software infrastructure was not capable of capturing DBTL cycle metrics. Spreadsheets were filled out to capture DBTL cycle metrics, but coverage was incomplete
- What was learned?: Focus on cycle time underweighs other aspects (sample throughput, resource intensity, number of cycles needed). Metrics need to cover various combinations of unit operations; analogies to EPA mileage estimates helpful. Software infrastructure can be developed to more automatically capture some metrics. DBTL cycle metrics are only one leading indicator of progress towards the ABF's goal (reducing bioprocess commercialization time)
- What changes will be made?: Software infrastructure will continue to be developed to capture DBTL cycle metrics. Other leading indicator metrics will also be investigated to evaluate progress towards the ABF's goal

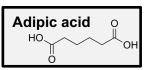




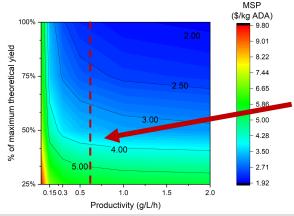
## **Transition from TRY to TEA and GHGs**

- What happened?: In FY20-FY22 Merit Review proposal, we originally had metrics related to annual TRY improvements
- What was learned?: Improvements to certain T, R, or Y metrics were the metrics, but they were not necessarily uniformly impactful from a TEA or LCA perspective, thus diverting resources from impactful research
- What changes will be made?: We changed our approach to focus on TEA and GHG emissions vis-à-vis fossil-based products that we are trying to displace, instead of uniform TRY metrics





Yield as the main driver of environmental performance



Diminishing returns upon further rate enhancements

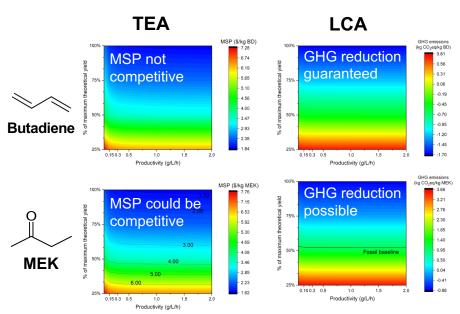




# **Integrated Analysis**

- What happened? Molecules of interest without direct market use need to undergo additional processing (e.g., catalytical upgrading) to molecules with larger markets
- What was learned? Comparative TEA/ LCA results are highly dependent on the choice of the comparison baseline, i.e., fossil or conventional product in the market, as well as downstream processing steps (outside ABF scope)
- What changes will be made?

Only onboard molecules directly of interest to industry via industry partnerships



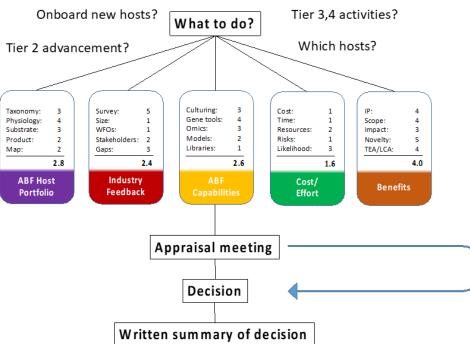
TEA and LCA results for two different end products derived from 2,3-butanediol: butadiene and methyl ethyl ketone



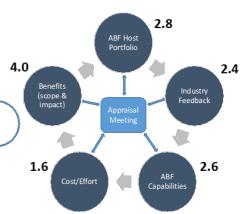


# Host breadth vs depth

#### Appraisal framework for host selection and prioritization



- What happened?: We had an ongoing question regarding whether we should focus on breadth (more organisms onboarded) or depth of organism development (higher tiers). Surveyed external stakeholders
- What was learned?: Received relatively even split opinions on breadth or depth



- What changes will be made?
  - Continue to put some resources towards new hosts. Need application to drive higher Tiers





## **Bioprocess Round Robins**

- What happened?: Glucose utilization was 25% higher in Emeryville with a 20% increase in muconic acid titer. Designed a study to eliminate sources of variability other than altitude. Triplicate 1.5 L-scale studies in Golden and Emeryville:
  - 1. Bioreactors with same aspect ratio
  - Batch mode to minimize stochastic variability that amplifies over longer fermentations
  - 3. Same water (shipped from Golden to Emeryville)
  - 4. Same glycerol stock
- What was learned?: Glucose utilization again higher in Emeryville, but muconic acid titers were similar
- What changes will be made?: Dissolved oxygen measurements do not replicate
  well between altitudes. Set points will be calibrated at sea-level. Pressure
  difference can also affect fermentation. Back pressure will be applied in largescale fermentations





## Further engaging and extracting value from IAB

- What happened?: Routine 1:1 discussions with Industry Advisory Board concerning (i) willingness to continue to serve, (ii) suggestions on improved meeting format, and (iii) diversity discovery
- What was learned?: Simple changes to meeting format and presentation content/style could lead to more productive and efficient quarterly interactions
- What changes will be made?
  - Include additional background information and "why" slides in presentations to allow members to engage early and formulate questions
  - -End each presentation with a slide that lists specific questions for the board
  - -Consider additional agenda items where Board presents (e.g. Diversity/ERG tools in companies, and industry panels for postdocs)
  - -FY22Q4 IAB meeting will be dedicated to meeting format discussions





# Collaboration process innovations & continuous improvement targets

- What happened?: Over 500 days average agreement development time for 2017 collaborative projects and protracted CRADA negotiation
- What was learned?: A key (but not sole) contributor to the slow CRADA execution was improved as a function of the implementation of a nonnegotiable CRADA, resulting in a 200 day decrease in average agreement development time
- What changes will be made?: Continued use of the non-negotiable CRADA, along with time restriction for development of SOW and background IP document, may further reduce the CRADA development time. ABF has implemented many other process improvements to improve collaborations. Many more are under review, to meet the needs of ABF's rapidly evolving collaboration mechanisms





		Further
What Worked Well	# Miro Votes	Discussion?
Tool development and engineering		N
Multi-omics capabilities	9	N
Multi-scale process and pathway development		N
ABF as a recognized brand	6	N
Software data infrastructure	6	N
Workforce development	6	N
Great work environment	6	N
Stability and reliability of work relationships	6	N
Automation of methods and processes	5	N
Working relationships / collaborations between ABF national Labs	4	N
Scientists and researchers work on projects outside the ABF	4	N
Al / ML tools and capabilities	4	N
Organizational Culture	3	N
Quarterly reporting to track progress	3	N
Relationship with DOE EERE, BETO TMs and Leadership	3	N
Capabilities and resources	3	N



		Further
What Worked Well	# Miro Votes	Discussion?
Recognition among industry		N
Stability and reliability of enterprise (relative to private sector)		N
ABF website and social media channels		N
Large datasets	1	N
Interest from industry (DFO oversubscription)	1	N
High impact of publications		N
Demonstration of near-industrially relevant TRY for several products		N
Reusable, useful, reproducible Learn algorithms such as ART and Bayesian MCA		N
Partnership / collaboration with NSF		N
Participation in Global Biofoundries Alliance		N
Distributed bioprocess development		N
Productive relationships with DOE Osc, BER BRCs, EMSL, JGI		N
Communication of progress		N
Teamwork		N
Strong collaborative relationships within ABF		N

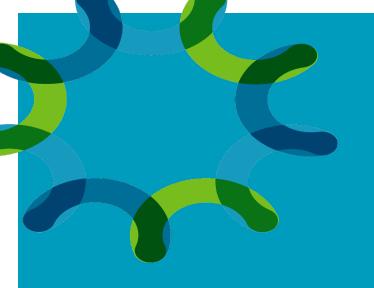


	# Miro	
What Didn't Work As Well	Votes 💷	Priorit 🖵
Integration of data infrastructure into workflows		Υ
Measuring performance improvement	8	Υ
Standard quantifiable practices	7	Υ
	6	v
Lack of widespread use of disruptive capabilities (automation and AI)		Υ
Method and process standardization		Υ
Data quality standards		Υ
Staff retention		Υ
Communication of ABF value proposition for industry projects		Υ
Communication of nuanced / complex metrics to BETO leadership	3	Υ
Learn resourcing		Υ
Large scale team work		Υ
Speed of experimental activities		Υ
Showing direct connection of infrastructure contributions to metrics /		
goals BETO cares about	2	Υ
Automation of methods and processes	2	Υ
Contracting with external partners		Υ
Alignment with industry needs		Υ



	# Miro	
What Didn't Work As Well	Votes 🚚	Priorit 📮
Communication of progress	2	Υ
IP licensing efficiency	2	Υ
Time required to develop DFO proposals with industry partners		Υ
Too much automation in areas that can be outsourced (e.g., plasmid		
construction) not enough inareas that can't (e.g., strain construction		
and evaluation)	1	Υ
People taking advantage of automation capabilities	1	Υ
Product portfolio focus		Υ
Learn connection	1	Υ
DBTL cycle tracking	1	N
Demonstrating advantage of ABF technologies without adequate		
comparison to alternative approaches	1	Υ
A centralized LIMs system to track projects and simplify procedures		
for users	1	N
Work prioritization		Υ
Scalability of collaborator coordination calls		Υ
DBTL cycle time as a proxy for industry value / impact		N





# 3 – Impact

### Impact on state of technology/industry if successful

#### Lessons Learned

 The lessons learned from the past 7 years of ABF operations will help guide the strategic and implementation planning process, which in turn will determine how the future ABF impacts the state of technology and industry

#### Future Plans

- As mentioned in the Project History, in September 2022, BETO instructed the ABF to primarily focus FY23Q1
  efforts on strategic planning and FY23Q2 on implementation planning, to re-envision and re-direct future ABF
  activities
- The genesis of this instruction was multi-faceted, but ABF and BETO lessons learned, along with a changing world and BETO goals, were important contributors
- The instruction included representative, and adjustable, vision and deliverables for the re-imagined ABF, along with directives concerning the formation of working groups and timelines
- The following presentations will focus exclusively on ABF's future plans





# **Summary**

- Goal: Apply ABF's past lessons learned, along with the efforts of the reviewing history working group, to inform and guide the development of the revised ABF strategic plan
- Relevance to BETO's goals: This activity, both instructed by BETO
  and a common sense best practice, ensures that the ABF's future
  plans are made wisely
- Outcomes: Past lessons learned used when undertaking a strategic re-envisioning of the large multi-lab ABF consortium project with a significant history and established identity in the community, so the ABF can have measurable and significant impact with an improved ability to communicate how the ABF is meeting big picture goals





## **Quad Chart Overview**

#### **Timeline**

• Project start: October 1, 2022

• Project end: September 30, 2025

	FY23 Costed	Total Award
DOE Funding	(10/01/2022 – 9/30/2023)	\$15M
Project Cost Share		

TRL Range: 2-4

#### **Project Goal**

Develop biomanufacturing tools, processes, and partnerships that enable sustainable industrial production of renewable fuels and chemicals for the nation

#### **End of Project Milestone**

- Transfer strains and bioprocesses for SAF and biochemicals to industry at industrially relevant titers, rates, and yields and at 70% reduction in GHG emissions relative to fossil-based production.
- Achieve 5% of ABF's annual budget as funds-in support, and based on learnings, strategize paths to future expansion
- Demonstrate at least 6 new technologies across Design (including TEA/LCA), Build, Test (including scale-up), and Learn

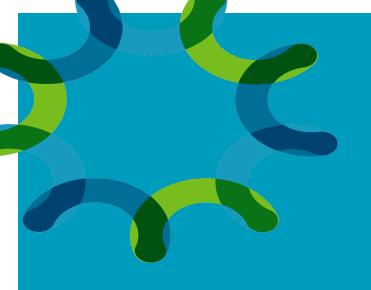
Funding Mechanism

#### **Project Partners**

LBNL (23%), SNL (20%), NREL (18%), PNNL (17%), LANL (8%), ORNL (8%), ANL (6%)







# **Additional Slides**

#### Publications, Patents, Presentations, Awards, and Commercialization

#### 70 publications, 189 presentations to date

- 54 publications and 115 presentations since FY2019
- The following slides list these publications and presentations

#### 17 patents, 10 records of invention, 9 software disclosures, & 2 licenses

• The following slides list these intellectual property assets





- Garima Goyal, Zak Costello, Jorge Alonso Guitierrez, Aram Kang, Taek Soon Lee, Hector Garcia Martin, and Nathan J Hillson. (2018) "Parallel Integration and Chromosomal Expansion of Metabolic Pathways" ACS Synthetic Biology DOI: 10.1021/acssynbio.8b00243
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- Oyetunde, T., Liu, D., Martin, H. G., & Tang, Y. J. "Machine learning framework for assessment of microbial factory performance." PloS one 14.1: e0210558 (2019).
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- Costello, Zak, and Hector Garcia Martin. "How to Hallucinate Functional Proteins." arXiv preprint arXiv:1903.00458 (2019).
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- Christopher B. Eiben, Tristan de Rond, Clayton Bloszies, Jennifer Gin, Jennifer Chiniquy, Edward E. K. Baidoo, Christopher J. Petzold, Nathan J. Hillson, Oliver Fiehn, Jay D. Keasling. (2019) "Mevalonate Pathway Promiscuity Enables Noncanonical Terpene Production", ACS Synth. Biol. https://doi.org/10.1021/acssynbio.9b00230
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- Isabel Pardo‡, Ramesh Jha‡, Molly Gaddis, Ryan Bermel, Felicia Bratti, Molly Gaddis, Emily McIntyre, William E. Michener, Ellen L. Neidle, Taraka Dale, Gregg T. Beckham\*, Christopher W. Johnson\*, Gene amplification, laboratory evolution, and biosensor screening reveal MucK as a terephthalic acid transporter in Acinetobacter baylyi ADP1, Metabolic Eng. (2020), 62, 260-274.
- Joshua R. Elmore, Gara N. Dexter, Davinia Salvachúa, Marykate O'Brien, Dawn M. Klingeman, Kent Gorday, Joshua K. Michener, Darren J. Peterson, Gregg T. Beckham, Adam M. Guss\*, Engineering Pseudomonas putida simultaneously catabolizes five major components of lignocellulosic biomass: Glucose, xylose, arabinose, p-coumaric acid, and acetic acid, Metabolic Eng. (2020), 62, 62-71.





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- Riley LA and Guss AM\*. Approaches to genetic tool development for rapid domestication of non-model microorganisms. Biotechnol (2021) 14:30. doi: 10.1186/s13068-020-01872-z.
- Somtirtha Roy, Tijana Radivojevic, Mark Forrer, Jose Manuel Marti, Vamshi Jonnalagadda, Tyler Backman, William Morrell, Hector Plahar, Joonhoon Kim, Nathan Hillson, and Hector Garcia Martin. (2021) "Multiomics Data Collection, Visualization, and Utilization for Guiding Metabolic Engineering". Frontiers in Bioengineering and Biotechnology 9, 45. DOI=10.3389/fbioe.2020.01009



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- Hector A. Plahar, Thomas N. Rich, Stephen D. Lane, William C. Morrell, Leanne Springthorpe, Oge Nnadi, Elena Aravina, Tiffany Dai, Michael J. Fero, Nathan J. Hillson, and Christopher J. Petzold. (2021) BioParts-A Biological Parts Search Portal and Updates to the ICE Parts Registry Software Platform" ACS Synthetic Biology DOI: 10.1021/acssynbio.1c00263"
- Chen Ling, George L. Peabody, Davinia Salvachúa, Young-Mo Kim, Colin M. Kneucker, Michela A. Monninger, Nathalie Munoz, Brenton C. Poirier, Kelsey J. Ramirez, Peter C. St. John, Sean P. Woodworth, Jon K. Magnuson, Kristin E. Burnum-Johnson, Gregg T. Beckham\*, Adam M. Guss,\* Christopher W. Johnson,\* Muconic acid production from glucose and xylose in Pseudomonas putida KT2440 via evolution and metabolic engineering, in review at Nature Comm.





- Nicholas A. Rorrer,‡ Sandra F. Notonier,‡ Brandon C. Knott,‡ Brenna A. Black,‡, Avantika Singh,‡ Scott R. Nicholson,‡ Christopher P. Kinchin, Graham P. Schmidt, Alberta C. Carpenter, Kelsey J. Ramirez, Christopher W. Johnson, Davinia Salvachúa, Michael F. Crowley, Gregg T. Beckham\*, Production of B-ketoadipic acid from glucose in Pseudomonas putida KT2440 for use in performance-advantaged nylons, in review at Cell Reports Phys. Sci.
- Precise genomic riboregulator control of metabolic flux in microbial systems. Naresh Pandey, Steffi A. Davison, Malathy Krishnamurthy, Daniel Trettel, Chien-Chi Lo, Shawn Starkenburg, Katherine L. Wozniak, Theresa Kern, Sean D. Reardon, Clifford J. Unkefer, Scott P. Hennelly and Taraka Dale. Submitted to ACS Synthetic Biology December 2021.
- Chen Y, Kaplan Lease N, Gin JW, Ogorzalek TL, Adams PD, Hillson NJ, et al. (2022) Modular automated bottom-up proteomic sample preparation for high-throughput applications. PLoS ONE 17(2): e0264467. https://doi.org/10.1371/journal.pone.0264467



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  Biology 2022 11 (2), 522-527 DOI: 10.1021/acssynbio.1c00324
- Hyun Gyu Lim, Kevin Rychel, Anand V. Sastry, Gayle J. Bentley, Joshua Mueller, Heidi S. Schindel, Peter E. Larsen, Philip D. Laible, Adam M. Guss, Wei Niu, Christopher W. Johnson, Gregg T. Beckham, Adam M. Feist, Bernhard Palsson, Machine-learning from Pseudomonas putida KT2440 transcriptomes reveals its transcriptional regulatory network, Metabolic Eng. (2022) 72, 297-310.
- Lim HG, Rychel K, Sastry AV, Bentley GJ, Mueller J, Schindel HS, Larsen PE, Laible PD, Guss AM, Niu W, Johnson CW, Beckham GT, Feist AM, Palsson BO. Machine-learning from Pseudomonas putida KT2440 transcriptomes reveals its transcriptional regulatory network. Metab Eng. 2022 Jul;72:297-310. doi: 10.1016/j.ymben.2022.04.004. Epub 2022 Apr 27.





- Chen Ling, George L. Peabody, Davinia Salvachúa, Young-Mo Kim, Colin M. Kneucker, Michela A. Monninger, Nathalie Munoz, Brenton C. Poirier, Kelsey J. Ramirez, Peter C. St. John, Sean P. Woodworth, Jon K. Magnuson, Kristin E. Burnum-Johnson, Adam M. Guss,\* Christopher W. Johnson,\* Gregg T. Beckham\*, Muconic acid production from glucose and xylose in Pseudomonas putida KT2440 via evolution and metabolic engineering, Nature Comm. (2022) 13, 4925
- Hector Garcia Martin\*, Tijana Radivojevic, Jeremy Zucker, Kristofer Bouchard, Jess Sustarich, Sean Peisert, Dan Arnold, Nathan Hillson, Gyorgy Babnigg, Jose Manuel Marti, Christopher J. Mungall, Gregg T. Beckham, Lucas Waldburger, James Carothers, ShivShankar Sundaram, Deb Agarwal, Blake A. Simmons, Tyler Backman, Deepanwita Banerjee, Deepti Tanjore, Lavanya Ramakrishnan, Anup Singh, Perspectives for self-driving labs in synthetic biology, submitted to Curr. Opin. Biotech
- N. Pandey, S.A. Davison, M. Krishnamurthy, D.S. Trettel, C. Lo, S. Starkenburg, K.L. Wozniak, T.L. Kern, S.D. Reardon, C.J. Unkefer, S.P. Hennelly and T. Dale. 2022. Precise genomic riboregulator control of metabolic flux in microbial systems. ACS Syn. Biol https://doi.org/10.1021/acssynbio.1c00638





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- Kyle R. Pomraning; Shuang Deng; Joonhoon Kim; Kristen B. Campbell; Ana L. Robles; Beth Hofstad; Nathalie Munoz; Yuqian Gao; Teresa Lemmon; Marie S. Swita; Jeremy D. Zucker; Young-Mo Kim; Kristin E. Burnum-Johnson; Jon K. Magnuson; Ziyu Dai. 2022 "Metabolic engineering to improve production of 3-hydroxypropionic acid from corn-stover hydrolysate in Aspergillus species." Metabolic Engineering
- Kevin J. McNaught, Eugene Kuatsjah, Michael Zahn, Érica T. Prates, Huiling Shao, Gayle J. Bentley, Andrew R. Pickford, Josephine N. Gruber, Kelley V. Hestmark, Daniel A. Jacobson, Brenton C. Poirier, Chen Ling, Myrsini San Marchi, William E. Michener, Carrie D. Nicora, Jacob N. Sanders, Caralyn J. Szostkiewicz, Dušan Veličković, Mowei Zhou, Nathalie Munoz, Young-Mo Kim, Jon K. Magnuson, Kristin E. Burnum-Johnson, K.N. Houk, John E. McGeehan, Christopher W. Johnson, Gregg T. Beckham, "Initiation of fatty acid biosynthesis in Pseudomonas putida KT2440", Metabolic Engineering, Volume 76, 2023, Pages 193-203, https://doi.org/10.1016/j.ymben.2023.02.006





- Gregg Beckham, Hybrid biological and catalytic processes to manufacture and recycle plastics,
   Princeton University, November 28th, 2018
- Nathan J. Hillson. "DOE Agile BioFoundry Overview". Invited Talk, SynBioBeta 2018 visit to ESE, Emeryville, CA, October 1, 2018
- Nathan J. Hillson. "Recent developments at the U.S Department of Energy Agile BioFoundry".
   Invited Talk, 2nd Darmstadt RoboWorkshop, Darmstadt, Germany, November 7, 2018
- Nathan J. Hillson. "DIVA (DNA Design, Implementation, Validation Automation) Platform".
   Invited Talk, 2nd Darmstadt RoboWorkshop, Darmstadt, Germany, November 8, 2018
- Garcia Martin, H. "Towards a predictive synthetic biology enabled by machine learning and automation". Ginkgo Bioworks, Boston, MA, November 12, 2018; AIChE annual meeting, Pittsburgh, PA, October 31 2018; Thermo Fisher, San Jose, CA, October 19, 2018; DTRA Tech Watch, Ft. Belvoir, VA, October 10, 2018.
- Garcia Martin, H. "A New Approach to Flux Analysis". ABF Annual Meeting, Berkeley CA, September 7, 2018.
- Nathan J. Hillson. "BioDesign Department Overview". Invited Talk, BSE Annual Meeting, Berkeley, CA, January 24, 2019





- Nathan J. Hillson. "Agile BioFoundry Overview". Invited Talk, BETO Peer Review, Denver, CO, March 7, 2019
- Nathan J. Hillson. "Agile BioFoundry DBTL Infrastructure". Invited Talk, BETO Peer Review, Denver, CO, March 7, 2019
- Nathan J. Hillson. "DNA Synthesis Science at the U.S. DOE Joint Genome Institute: Biosecurity Sequence Screening and Broader Aspects Review". Invited Talk, EBRC Spring Retreat 2019, Boston, MA, March 23, 2019
- Nathan J. Hillson. "ABF: plans for the next 3-year cycle". Invited Talk, BETO Quarterly FY19Q2, Washington DC, March 27, 2019
- Jennifer Chiniquy. "Emery Station East DIVA DNA Sequencing". Invited Talk, BSE Annual Meeting, Berkeley, CA, January 24, 2019
- Garcia Martin, H. "Towards a predictive synthetic biology enabled by machine learning and automation". EmeryStation Campus, Emeryville, CA, February 7th, 2019.
- Garcia Martin, H. "Metabolic modeling, drug synthesis, and their interaction". LBNL Biosciences Experts Advisory Committee, Berkeley, CA, February 8th, 2019.
- Garcia Martin, H. "Towards a predictive synthetic biology enabled by machine learning and automation". Google X, Mountain View, CA, February 14th, 2019.





- Garima Goyal, Z. Costello, J.A. Gutierrez, A. Kang, T.S. Lee, H.G. Martin, and N.J. Hillson.
   "PIACE: Parallel Integration and Chromosomal Expansion of metabolic Pathways". Invited Talk, ACS Conference, Orlando, Florida, April 4, 2019
- Nathan J. Hillson. "DNA synthesis use and biosecurity screening at U.S. DOE projects including the Joint Genome Institute, Joint BioEnergy Institute, and Agile BioFoundry". Invited Talk, Gene Synthesis Governance Meeting, Johns Hopkins Center for Health Security, St. Regis Hotel, Washington, DC, April 9, 2019
- Nathan J. Hillson. "DOE Agile BioFoundry: Overview and Recent Highlights". Invited Talk, SBFC 2019 Session ST-2: Global Research Consortia, Seattle, WA, May 1, 2019
- Nathan J. Hillson. "2019 BETO Merit Review Process". Invited Talk, ABF IAB FY19Q3, Zoom Videoconference, May 17, 2019
- Nathan J. Hillson. "Machine Learning-assisted MiSeq library loading". Invited Talk, ABF IAB FY19Q3, Zoom Videoconference, May 17, 2019
- Nathan J. Hillson. "Global Biofoundries Alliance: 2019 Annual Meeting Report Out". Invited Talk, ABF IAB FY19Q3, Zoom Videoconference, May 17, 2019
- Nathan J. Hillson. "2019 BETO Peer Review Report Out". Invited Talk, ABF IAB FY19Q3, Zoom Videoconference, May 17, 2019





- Nathan J. Hillson. "ICE/DIVA, EDD, and ART". Invited Talk, Software for Synthetic Biology Workflows Workshop, SEED 2019, New York, NY, June 27, 2019
- Nathan J. Hillson. "DOE Agile BioFoundry: Overview and Recent Highlights". Invited Talk, JBEI Annual Meeting 2019, Monterrey, CA, May 30, 2019
- Henrique C. De Paoli. "Overview of Synthetic Biology principles". Invited Talk, Xu's Research Group, UC Dept. of Materials Science and Engineering, Berkeley, CA, May 13, 2019.
- Nathan J. Hillson "ABF: CRADA updates and FY20-22". Invited Talk, BETO Conversion Call, July 1, 2019
- Wei Xiong and Nathan Hillson, "Synthetic C1 Condensation Cycle for Formate-Mediated ElectroSynthesis". Invited Talk, BETO Conversion Call, July 8, 2019
- Ernst Oberortner, Nathan J. Hillson, and Jan-Fang Cheng. "The Operon Refactoring and Construction Assistant (ORCA): Streamlined gene cluster refactoring". Invited Talk, 11th International Workshop on Bio-Design Automation, University of Cambridge, UK July 9, 2019
- Nathan J. Hillson "ABF Overview, FY19 Update, and FY20-22 Plans". Invited Talk, ABF Annual Meeting, Richland, WA, July 30, 2019
- Nathan J. Hillson "FY22Q4\_DBTL\_AS1: 5x efficiency improvements". Invited Talk, ABF Annual Meeting, Richland, WA, July 31, 2019





- Nathan J. Hillson "DOE Agile BioFoundry: Overview and Recent Highlights". Invited Talk, VIP Visit - Wendy Pulling | Director of ESG Integration University of California Office of the Chief Investment Officer, Emeryville, CA, Aug 6, 2019
- Nathan J. Hillson "DOE Agile BioFoundry: Overview and Recent Highlights". Invited Talk, Tiangong Forum Distinguished Lecture, Tianjin Institutes of Industrial Biotechnology (TIB), Chinese Academy of Sciences (CAS), Tianjin, China, August 16, 2019
- Nathan J. Hillson "DOE Agile BioFoundry: DBTL Infrastructure". Invited Talk, SynBioYSF 2019, Tianjin Institutes of Industrial Biotechnology (TIB), Chinese Academy of Sciences (CAS), Tianjin, China, August 17, 2019
- Nathan J. Hillson "U.S. DOE Agile BioFoundry: Overview and Recent Highlights", Invited Talk, Genscript Double Helix Symposium 2019, San Francisco, CA September 30, 2019
- Jennifer Chiniquy "DIVA DNA Sequencing". Invited Talk, 2019 ABF All Hands Meeting, Pacific Northwest National Laboratory, Richland, WA, July 30, 2019.
- Tijana Radivojevic, "Automatic Recommendation Tool", Invited Talk, ABF Annual Meeting 2019, Richland, WA, July 30, 2019
- Nurgul Kaplan."Automated DNA Construction: "from j5 protocol design to Laboratory Robotics" Invited Talk, ABF Annual Meeting 2019, Pasco, WA, July 30, 2019





- Nathan J. Hillson "U.S. DOE Agile BioFoundry: Organization and Capabilities", Invited Talk, ABF Industry Day 2019, Emeryville, CA October 4, 2019
- Garcia Martin, H. "Machine Learning, Synthetic Biology and Automation: Engineering Life for the Benefit of Society". NERSC data seminar, Berkeley CA, November 1st, 2019.
- Garcia Martin, H. "ART: a machine learning Automated Recommendation Tool for guiding synthetic biology". Al4Synbio Symposium, Arlington VA, November 8th, 2019.
- Garcia Martin, H. "Opportunities in the intersection of:Artificial Intelligence & Synthetic Biology & Automation". Army Science Planning and Strategy Meeting, Burlington MA, November 13th, 2019.
- Nathan J. Hillson "ABF: CRADA updates and FY20-22". Invited Talk, BETO Conversion Call, July 1, 2019
- Wei Xiong and Nathan Hillson, "Synthetic C1 Condensation Cycle for Formate-Mediated ElectroSynthesis". Invited Talk, BETO Conversion Call, July 8, 2019
- Ernst Oberortner, Nathan J. Hillson, and Jan-Fang Cheng. "The Operon Refactoring and Construction Assistant (ORCA): Streamlined gene cluster refactoring". Invited Talk, 11th International Workshop on Bio-Design Automation, University of Cambridge, UK July 9, 2019





- Nathan J. Hillson "ABF Overview, FY19 Update, and FY20-22 Plans". Invited Talk, ABF Annual Meeting, Richland, WA, July 30, 2019
- Nathan J. Hillson "FY22Q4\_DBTL\_AS1: 5x efficiency improvements". Invited Talk, ABF Annual Meeting, Richland, WA, July 31, 2019
- Nathan J. Hillson "DOE Agile BioFoundry: Overview and Recent Highlights". Invited Talk, VIP Visit - Wendy Pulling | Director of ESG Integration University of California Office of the Chief Investment Officer, Emeryville, CA, Aug 6, 2019
- Nathan J. Hillson "DOE Agile BioFoundry: Overview and Recent Highlights". Invited Talk, Tiangong Forum Distinguished Lecture, Tianjin Institutes of Industrial Biotechnology (TIB), Chinese Academy of Sciences (CAS), Tianjin, China, August 16, 2019
- Nathan J. Hillson "DOE Agile BioFoundry: DBTL Infrastructure". Invited Talk, SynBioYSF 2019, Tianjin Institutes of Industrial Biotechnology (TIB), Chinese Academy of Sciences (CAS), Tianjin, China, August 17, 2019
- Nathan J. Hillson "U.S. DOE Agile BioFoundry: Overview and Recent Highlights", Invited Talk, Genscript Double Helix Symposium 2019, San Francisco, CA September 30, 2019
- Jennifer Chiniquy "DIVA DNA Sequencing". Invited Talk, 2019 ABF All Hands Meeting, Pacific Northwest National Laboratory, Richland, WA, July 30, 2019.





- Tijana Radivojevic, "Automatic Recommendation Tool", Invited Talk, ABF Annual Meeting 2019, Richland, WA, July 30, 2019
- Nurgul Kaplan."Automated DNA Construction: "from j5 protocol design to Laboratory Robotics"
   Invited Talk, ABF Annual Meeting 2019, Pasco, WA, July 30, 2019
- ART: A machine learning Automatic Recommendation Tool for guiding synthetic biology",
   Invited Talk, Computational Bio-Science Meeting, Berkeley, CA, April 23, 2020
- Garcia Martin, H. "Opportunities in the intersection of machine learning, synthetic biology, and automation". ABLC 2020, Virtual meeting, July 10th, 2020.
- Garcia Martin, H. "Leveraging machine learning and automation to make synthetic biology predictable". SPIE Optics + Photonics 2020, Virtual meeting, August 24th, 2020.
- Nathan J. Hillson, "FY20 ABF CRADA Call: Process, Applications, and Selections", Conversion R&D Standing Lab Update Call, via WebEx, July 27, 2020
- Nathan J. Hillson, "Perspectives from the U.S. DOE Agile BioFoundry", OECD BNCT Virtual Workshop, Session 1: Biofoundries and COVID-19, via Zoom, July 29, 2020
- Nathan J. Hillson, "DIVA, EDD, and ART: Software spanning the Design/Build/Test/Learn cycle", invited talk, COMBINE 2020, via Zoom, October 5, 2020





- Nathan J. Hillson, "DIVA, EDD, and ART: Software spanning the Design/Build/Test/Learn cycle", invited talk, SPARC Workshop (IIT Kharagpur) 2020, via Zoom, October 19, 2020
- Invited talk: Guss AM. "Domestication of non-model microbes for the production of renewable fuels and chemicals" (2021) The Metabolic Engineering Virtual Seminar Series at the University of Texas-Austin. Virtual.
- Garcia Martin, H. "Leveraging machine learning and automation to make bioengineering predictive". The Metabolic Engineering Virtual Seminar, UT Austin, February 12th, 2021.
- Garcia Martin, H. "Machine Learning for Bioengineering". JBEI Board of Directors, March 12th, 2021.
- Nathan J. Hillson, "ABF Overview", invited talk, BETO Peer Review 2021, via Zoom, March 9, 2021
- Nathan J. Hillson, "ABF DBTL Infrastructure", invited talk, BETO Peer Review 2021, via Zoom, March 9, 2021
- Nathan J. Hillson, "ABF Overview", invited talk, BSA ExComm, via Zoom, March 12, 2021
- Guss AM. "Synthetic biology and metabolic engineering of non-model microbes for the production of renewable fuels and chemicals" Seminar at Purdue University Northwest. April 16, 2021.





- Radivojevic, T., "Automated Recommendation Tool (ART): Design of Experiments via Probabilistic Predictive Modeling", Autonomous Discovery in Science and Engineering Workshop, April 21, 2021(Invited Tutorial)
- Radivojevic, T., "Guiding synthetic biology via machine learning", Symposium on Biomaterials,
   Fuels and Chemicals (SBF): Speeding up synthetic biology, April 27, 2021
- Radivojevic, T., "Guiding synthetic biology via Automated Recommendation Tool (ART)", Synthetic Biology: Engineering, Evolution & Design (SEED) 2021, Computation, Artificial Intelligence, and Machine Learning for Biological Design Session, June 17, 2021 (Invited Speaker)
- Guss AM. "Domestication of non-model microbes for the production of renewable fuels and chemicals" Student-invited seminar at North Carolina State University. September 27, 2021.
- Radivojevic, T. "Guiding synthetic biology via machine learning and multi-omics technologies", IWBDA 2021, 13th International Workshop on Bio-Design Automation, September 20, 2021 (virtual)
- Hillson, Nathan J. "Session Introduction", Metabolic Engineering 14, Block 8: Session Biofoundries, (Virtual via Remo), July 15, 2021





- Hillson, Nathan J. "Updates on DOE assets including Agile BioFoundry, Joint BioEnergy Institute, and Joint Genome Institute", Digital Biology Engineering Meeting (Air Force) via zoom, September 23, 2021
- Garcia Martin, H. "Machine Learning Tools Can Make Synthetic Biology Predictable". SIMB, August 9th, 2021.
- Garcia Martin, H. "Leveraging machine learning and automation to make bioengineering predictable". Indo-US Workshop on Application of Data Science in Biological Systems, September 7th, 2021.
- Garcia Martin, H. "Leveraging machine learning and automation to make bioengineering predictable". Air Force Research Laboratory MIrACLE Forum, September 10th, 2021.
- Garcia Martin, H. "Challenges and opportunities in high-throughput data synthesis". NSF
  Challenges and Opportunities in Synthesizing Massively Parallel Assays and High-Throughput
  Datasets Workshop, September 17th, 2021.
- Garcia Martin, H. "Guiding metabolic engineering via kinetic deep learning and multi-omics".
   Quantitative Modelling of Cell Metabolism Conference, September 21th, 2021.
- Davison, S. Reprogramming Microbes for Biomanufacturing, Science in 3 at Los Alamos National Laboratory, September 2021





- Wozniak, K. Engineering a Sustainable Future: Fine-tuning Gene Expression for Biomanufacturing, Science in 3 at Los Alamos National Laboratory, September 2021
- Davison, S. Fine-tuning gene expression in bioproduction pathways in diverse bacterial hosts,
   SIMB Annual Meeting, August.
- Wozniak, K. Targeting global regulatory responses using precise and programmable cisriboregulators SIMB Annual Meeting, August
- Adam Guss. "Genetic tools and microbial engineering for biological production of sustainable fuels and chemicals" Presented to Weekly Seminar for DOE CCI/SULI Students. October 27, 2021
- Adam Guss. "Domestication of diverse non-model microbes for plastics upcycling and sustainable fuel and chemical production" Biological Sciences Departmental Seminar, Michigan Technical University. Oct 28, 2021.
- Garcia Martin, H. "Guiding metabolic engineering via kinetic deep learning and multi-omics".
   Quantitative Modelling of Cell Metabolism Conference, October 20th, 2021.
- Garcia Martin, H. "Machine learning for industrial biotechnology". Delft Advanced Course Integrated Multi-Omics approaches for Improvement of Industrial Microbes, November 5th, 2021.





- Hillson, Nathan J. "Opportunities for CABBI collaboration with JBEI (and other DOE assets) in laboratory operations and data management infrastructure", CABBI seminar, via zoom, October 19, 2021
- Hillson, Nathan J. "Automation in Biotechnology: Challenges and Opportunities", Panelist at SENAI CETIQT (Brazil), via zoom, October 29, 2021
- Hillson, Nathan J. "ABF Overview and Capabilities", ABF Industry Day (via zoom), November 19, 2021
- Hector A Plahar, Stephen D. Lane, William C Morrell, Nathan J. Hillson and Christopher J. Petzold. "A Biological Parts Search Portal and Updates to the ICE Parts Registry Platform", JBEI Annual DOE Review, Dec 6-8, 2021
- Tijana Radivojevic, "Creating a Machine Learning Chassis to Maximize the Efficiency of the DBTL Cycle in Synthetic Biology", Synthetic Biology-Based Therapeutics Summit, December 9, 2021 (virtual)
- Hillson, Nathan J. "Overview and capabilities of the ABF and opportunities for collaboration with CSU", Colorado State Seminar Series (via zoom), February 3, 2022
- Hillson, Nathan J. "ABF prospective collaboration with other BETO consortia and projects", BETO Conversion Call (via MS Teams), March 7, 2022





- Bilbao, A. "Investigating deep learning approaches to advance data processing in Liquid Chromatography, Ion Mobility and Data-Independent Acquisition Mass Spectrometry Omics".
   70th ASMS Conference on Mass Spectrometry and Allied Topics, Minneapolis, Minnesota, June 9th, 2022.
- Dai Z., K.R. Pomraning, S. Deng, J. Kim, K.B. Campbell, A.L. Robles, and B.A. Hofstad, et al. 05/02/2022. "Assessment and Optimization of 3-hydroxypropionic acid production in industrial filamentous fungus-Aspergillus species." Presented by Z. Dai at 44th Symposium on Biotechnology for Fuels and Chemicals (SBFC 2022), New Orleans, Louisiana
- Adam Guss. "High efficiency DNA integration in diverse non-model microbes for rapid tool and pathway prototyping" SIMB SBFC. New Orleans, LA, May 3, 2022
- Magnuson, J.K.; Beckham, G.T.; Gladden, J.M.; Dale, T.; Guss, A.M.; Laible, P.; Hillson, N.J. 05/03/2022. "The Agile BioFoundry" Presented by Jon Magnuson at the 44th Symposium on Biotechnology for Fuels and Chemicals (SBFC 2022), New Orleans, Louisiana.
- Poirier, B.C. et al. "Mechanical cell disruption enhances the extraction of metabolites from bacterial and fungal species commonly used in metabolic engineering". 70th ASMS Conference on Mass Spectrometry and Allied Topics, Minneapolis, Minnesota, June 5-9, 2022.





- Poirier B.C. et al. "Behavior of lactam molecules during aqueous sample preparation and mass spectrometry analysis". 70th ASMS Conference on Mass Spectrometry and Allied Topics, Minneapolis, Minnesota, June 5-9, 2022.
- Hillson, Nathan J. "Overview and Capabilities of the DOE Agile BioFoundry", ABF Webinar (via zoom) April 29, 2022
- Hillson, Nathan J. "Overview and Capabilities of the DOE Agile BioFoundry", Lessafre visit to ESE (via zoom) May 6, 2022
- Hillson, Nathan J. "Overview and Capabilities of the DOE Agile BioFoundry" (Keynote Presentation) Bioindustry 4.0 – Synthetic Biology & Biofoundry, CHEY Institute – Scientific Innovation Series (via zoom) 12 May 17 (PDT) 18 (KST), 2022
- Hillson, Nathan J. "Overview and Capabilities of the DOE Agile BioFoundry", Wageningen University visit to ESE (via zoom) May 31, 2022
- Hillson, Nathan J. "ABF overview and DBTL Infrastructure", BETO Conversion Call (via MS Teams), June 13, 2022
- Nathan Hillson. "ABF Decarbonization Efforts", Invited Talk, LBL Carbon Negative Initiative –
   Biological Applications Lightning Talk Session (via zoom) 6/27/2022





- Radivojevic, Tijana. "Guiding synthetic biology via machine learning", Boston University, April 14, 2022, Guest lecture
- Deng S., J. Kim, K.R. Pomraning, Z. Dai, Y. Gao, N. Munoz Munoz, and Y. Kim, et al. 08/07/2022. "Identification of a specific exporter that enables high production of aconitic acid in A. pseudoterreus ATCC32359." Presented by S. Deng at SIMB annual meeting, San Francisco, California.
- Pomraning K.R., Z. Dai, S. Deng, N. Munoz Munoz, Y. Kim, B.A. Hofstad, and Y. Gao, et al. 08/10/2022. "Bioconversion of lignocellulosic feedstocks to 3-hydroxypropionic acid using acidophilic fungi." Presented by K.R. Pomraning at Society for Industrial Microbiology and Biotechnology, San Francisco, California.
- Jha RK. High throughput test tools for industrially relevant microbial chassis, SIMB 2022, San Francisco, August 2022 (invited talk).
- Adam Guss. "Using synthetic biology to solve challenges in plastic waste and renewable chemical production". Biological Sciences Departmental Seminar, Missouri S&T, Rolla, MO. September 27, 2022.
- Nathan Hillson. "Agile BioFoundry Connections with NSF, MSRDC, and Beyond", Invited Talk, LBL Biosciences Expert Advisory Committee: connections beyond Biosciences July 8, 2022





- Nathan Hillson. "Biosecurity concern anecdote", Screening Tools for Genome Engineering and Genome Editing (Inscripta-funded; Sarah Carter organized), via MS Teams, 9/9/2022
- Nathan Hillson. "Webinar Agenda and ABF Overview", ABF Webinar: Cutting-Edge
   Technologies for Accelerating Bioproduct Development at the Agile BioFoundry, 9/22/20222
- Garcia Martin, H. "Machine Learning and Automation for Predictive Synthetic Biology". Basque Center for Applied Mathematics, Bilbao, Spain, July 15th, 2022.



# License partners and patent applications

#### **Technologies licensed**

- Bioproduction of limonene from syngas
- Method to produce branched chain polyhydroxyalkanoates and branched chain 3-hydroxyacids

#### **Provisional Patents**

- ROI-18-92 U.S. provisional patent applications 63/163,518 63/321,207 63/479,918, not published
- ROI-21-104 U.S. provisional patent application 63/321,332
- ROI-21-63 U.S. provisional patent applications 63/163,518 63/321,207 63/479,918, not published

#### **Patent Applications**

- Post-transcriptional genome regulation in bacteria with next generation CRISPR-Cas tools
- · Terephthalate biosensor and applications thereof
- · Mutant transporters for bacterial uptake of terephthalic acid
- Alleviating the bottleneck in enzyme evolution and pathway optimization using novel biosensors (Disclosure Title) Modified Biosensors and Biocatalysts and Methods of Use (Application Title)
- Mutant transporters for bacterial uptake of terephthalic acid
- ART: A machine learning Automated Recommendation Tool for guiding synthetic biology





# Patent applications

#### **Patent Applications (cont.)**

- A Generative Model for Protein Sequences for the Purpose of Protein Design or Phenotypic Inference
- Predicting Metabolic Pathway Dynamics from Time Series Multiomics Data Using Machine Learning Techniques
- Use of Statistical Learn Approaches to Predict Next Generation Sequencing Subsequence Depth of Coverage
- Mutant transporters for bacterial update of terepthalic acid
- Method and strain for sugar conversion
- Engineered Microorganisms for the Production of Intermediates and Final Products (1st)
- Engineered Microorganisms for the Production of Intermediates and Final Products (2<sup>nd</sup>)
- Production of organic acids from Aspergillus pseduoterreus cadA deletion strain (1st)
- Production of organic acids from Aspergillus pseduoterreus cadA deletion strain (2<sup>nd</sup>)
- Genetically engineering an industrial filamentous fungus Aspergillus niger for 3hydroxypropionic acid production
- A specific exporter responsible for aconitic acid high production in Aspergillus pseduoterreus





#### Records of invention

#### **Records of Invention**

- Bioproduction of limonene from syngas
- Mutant transporters for bacterial update of terepthalic acid
- Method to produce branched chain polyhydroxyalkanoates and branched chain 3hydroxyacids
- A genetic circuit to reduce cell-to-cell production heterogeneity
- High yield conversion of D-xylose to D-arabitol in R. toruloides
- Manipulation of tRNA thiolation gene ncs2 for enhanced production of fatty-acyl-CoA derived chemicals in R. toruloides
- Efficient production of cis, cis-muconic acid from mixed substrates of glucose, D-xylose and L-arabinose
- Whole cell biosensors for industrially relevant polymers precursors
- Engineered Microorganisms for the Production of Intermediates and Final Products
- Method and strain for sugar conversion





## **Software disclosures**

#### **Software Disclosures**

- Automated Recommendation Tool (ART) v2.0
- Kinetic Learning v0.1
- Automated Recommendation Tool (ART): v1.0
- PIACE: Parallel Integration and Chromosomal Expansion of Metabolic Pathways
- OMG, Omics Mock Generator Library: v0.1.1
- Fermentation Data Processing
- Fermentation Data Manipulation and Analysis Once imported
- DIVA/Device Editor 3.1
- DIVA/Device Editor (DIVA) v6.0.0



